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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
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Michael Eppihimer, et al.) Group Art Unit: 1644
)
Serial No.: 09/825,580) Examiner: GAMBEL, P.
)
Filed: April 2, 2001) Confirmation No.: 9952
)
For: INHIBITION OF THROMBOSIS BY)
TREATMENT WITH P-SELECTIN)
ANTAGONISTS)

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY BRIEF UNDER 37 C.F.R. § 41.41

This paper is filed by Appellant under 37 C.F.R. § 41.41 in response to the
Examiner's Answer mailed October 18, 2007.

I. Status Of Claims

In response to the Appeal Brief filed July 6, 2007, the following rejections remain:

Claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57 stand rejected under 35 U.S.C. § 102(e) as inherently anticipated by U.S. Patent No. 5,464,778 ("Cummings") as evidenced by THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 1655 (17th ed. 1999) ("Merck Manual") and Lip *et al.*, "Hypertension and the prothrombotic state," *J. Hum. Hyper.* 14: 687-90 (2000) ("Lip"). Examiner's Answer, page 6. Appellant notes that claims 46 and 47 were previously withdrawn and those claims should not listed as rejected.

Claims 1-20, 25-27, 31-40, 45, and 50-57 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cummings and U.S. Patent No. 5,840,679 ("Larsen") in view of Blann *et al.*, "Evidence of platelet activation in hypertension," *J. Hum. Hyper.* 11:607-609 (1997) ("Blann"), U.S. Patent No. 6,150,348 ("Araneo") and, U.S. Patent No. 5,604,207 ("DeFrees"), and further in view of the Merck Manual and Lip.

The Office previously rejected claim 27 under 35 U.S.C. § 103(a) as allegedly unpatentable over Cummings, Larsen, Blann, Araneo, DeFrees, the Merck Manual, Lip, further in view of Maugeri *et al.*, "Polymorphonuclear leukocyte-platelet interaction: role of P-selectin in thromboxane B₂ and leukotriene C₄ cooperative synthesis," *Thromb. Haem.* 72:450-456 (1994) ("Maugeri") and Johnston *et al.*, "Differential roles of selectins and the α 4-integrin in acute, subacute, and chronic leukocyte recruitment in vivo," *J. Immunol.* 159:4514-4523 (1997) ("Johnston"). See Office Action, Mailed September 28, 2006, p. 10. The Examiner's Answer does not state that the rejection stands, but

discusses Maugeri and Johnston. See *e.g.*, Examiner's Answer, pages 31-32. Thus, Appellant discusses those publications and claim 27 in this Reply.

II. Argument

Appellant has carefully considered the Arguments set forth in the Examiner's Answer. Appellant provides the following arguments in response.

A. **The Office Fails to Apply the Proper Legal Standard for Anticipation**

In response to Appellant's arguments that claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57 are neither expressly nor inherently anticipated by Cummings, the Office maintains that Cummings inherently anticipates the claimed invention, and asserts that "the missing descriptive matter [from Cummings] of 'a subject having hypertension' was necessarily present in the targeted patient populations **and/or immediately envisaged** as target populations" Examiner's Answer, page 23 (emphasis added).

As discussed at length in the Appeal Brief filed on July 6, 2007 ("Appeal Brief), to find inherency, the matter that is not expressly disclosed by a reference must be necessarily present, and inherency cannot be demonstrated by mere possibility. Appeal Brief, pages 14-17; *see also* MPEP § 2112. What one of ordinary skill in the art would have "immediately envisaged" is inapposite.

The Office attempts to overcome the requirement of showing that hypertension was necessarily present in the subjects in Cummings by citing the Merck Manual and Lip, none of which demonstrate the necessary association. For example, the Office cites the Merck Manual to support the proposition that atherosclerosis "is consistent with hypertension." Examiner's Answer, p. 18. However, the question is not whether a condition is "consistent with hypertension" but rather whether it is necessarily present. As discussed in the Appeal Brief, the Merck Manual does not teach that hypertension is

necessarily present in atherosclerosis and does not even list hypertension as a symptom of atherosclerosis. Appeal Brief, pages 17-18.

The Office admits that “atherosclerosis may be characteristically silent until stenosis, thrombosis, aneurysm or embolus supervenes,” which is stated in the Merck Manual, but asserts that “the Merck Manual does not teach away” from the claimed method. Examiner’s Answer, page 18-19, bridging paragraph.

Appellant has not argued that Cummings fails to anticipate the claimed invention because the Merck Manual teaches away. The Merck Manual may teach away from the claimed invention. However, “whether a reference ‘teaches away’ from the invention is inapplicable to an anticipation analysis.” *Rasmussen v. SmithKline Beecham Corp.*, 75 U.S.P.Q.2d 1297, 1302-3 (Fed. Cir. 2005) (quoting *Celeritas Techs., Ltd. v. Rockwell Int’l Group*, 47 U.S.P.Q.2d 1516, 1522 (Fed. Cir. 1998)). Appellant has argued that the “silence” in the Merck Manual indicates that hypertension is not necessarily present in the conditions of Cummings and that Cummings does not inherently anticipate the claimed invention. See Appeal Brief, pages 17-18.

The Office’s reliance on Lip is similarly misplaced. As discussed in the Appeal Brief, Lip does not teach that hypertension is necessarily present in any condition disclosed by Cummings, but describes the relationship between hypertension and thrombosis as one of “risk.” Appeal Brief, pages 18-17. The Merck Manual also discusses risk factors. *Id.* at 18. The concept of “risk” reflects a probability that a certain condition may lead to another. Inherent anticipation does not rely on mere “probabilities or possibilities.” See MPEP § 2112. Accordingly, the discussion of risk

factors in Lip and the Merck Manual does not show that hypertension was necessarily present in the conditions of Cummings.

Appellant's understanding of the Merck Manual and Lip is supported by the declaration of Dr. Hemmerich, submitted on September 13, 2005 ("Declaration"). Hypertension need not coexist with atherosclerosis, stroke or transient ischemic attacks. See Declaration, Paragraphs 7 and 8 A-C.

For the reasons discussed above, and those in the Appeal Brief, Appellant respectfully asserts that the Office has failed to show that hypertension was necessarily present in Cummings, and that Cummings does not anticipate claims 1-4, 8-13, 16-18, 25-27, 45, 50-53 and 57.

B. The Office Has Not Shown That All the Elements of the Claims Are Present in Cummings

Appellant believes that the Office as failed to demonstrate that Cummings anticipates claims 1-4, 8-13, 16-18, 25-27, 45, 50-53 and 57, at least because hypertension is not necessarily present in Cummings. However, the Office also asserts that additional elements of those claims are present in Cummings. Specifically, the Office states that "the claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC₄) would have been inherent properties of the referenced methods" Examiner's Reply, page 6.

Appellant respectfully asserts that these additional elements are not expressly or necessarily present in Cummings. For example, Cummings did not disclose a nucleotide sequence encoding PSGL-1 and could not have engineered a soluble protein (claim 2), or a recombinant protein (claim 4). Cummings does not disclose any

nucleotide sequence encoding PSGL-1 including those of claims 8-13, 52, and 53. As stated by the Office, "Cummings *et al.* differs from the claimed PSGL by not disclosing particular human PSGL sequences and domain structure thereof." Examiner's Answer, page 10. Finally, Cummings does not disclose thrombus inducing agents, including LTC₄ (claims 25-27).

Accordingly, for these additional reasons, Appellant respectfully asserts that Cummings fails to anticipate at least claims 1, 4, 18-13, 25-27, 52 or 53.

III. The Office Fails to Demonstrate that the Claimed Invention Is *Prima Facie* Obvious

In response to Appellant's arguments that the claimed invention is non-obvious, the Office maintains the rejection and asserts "the missing descriptive matter of 'a subject having hypertension' was necessarily present in the targeted patient populations and/or immediately envisaged as target populations" Examiner's Answer, page 23.

As discussed above, and in the Appeal Brief on pages 17-29, Lip and the Merck Manual do not show that hypertension was necessarily present in the conditions of Cummings. On the contrary, one of skill in the art would not know whether a patient suffered from hypertension merely because they suffered from a condition such as atherosclerosis, because hypertension is not listed as a symptom by the Merck Manual. Similarly, the skilled artisan would not know if a patient suffering from hypertension also suffered from thromboses, and would have no reason to treat such a subject with PSGL-1.

In the Appeal Brief, Appellant provided a detailed analysis of the publications the Office asserts in its obviousness rejection, and why the combination of those publications would not have rendered the claimed invention obvious. See Appeal Brief,

pages 22-27. Appellant provides the following additional arguments regarding the publications cited against the claims.

A. Cummings

Cummings discusses treatment of conditions including atherosclerosis, stroke, and conditions produced by ischemia/reperfusion injury but does not teach that these conditions are necessarily associated with hypertension. See Cummings, col. 18, line 54 to col. 19, line 20, and col. 19, line 64 to col. 20, line 5. As discussed above, the Merck Manual and Lip fail to show that hypertension is necessarily present in the conditions of Cummings. Thus, those publications fail to cure the deficiencies of Cummings and would not have suggested to the artisan of ordinary skill that a composition having P-selectin ligand activity should be used to treat or inhibit thrombosis in a patient with hypertension.

B. Larsen

Larsen describes a P-selectin ligand protein but does not mention treatment of subjects with hypertension or that conditions treatable with P-selectin ligand are associated with hypertension. (See column 15, lines 50-66). As discussed above, the Merck Manual and Lip fail to show that hypertension is necessarily present in the conditions of Cummings. Similarly, the Merck Manual and Lip fail to show that hypertension is necessarily present in the conditions of Larsen. Thus, those publications fail to cure the deficiencies of Larsen and would not have suggested to the artisan or ordinary skill that a composition having P-selectin ligand activity should be used to treat or inhibit thrombosis in a patient with hypertension.

C. Lip

As discussed above, Lip does not teach that hypertension is necessarily present in any condition disclosed by Cummings, but describes the relationship between hypertension and thrombosis as one of "risk." Accordingly, Lip does not cure the deficiencies of Cummings because one of ordinary skill in the art would not know whether a patient suffering from a condition disclosed in Cummings also had hypertension. Therefore, the combination of Lip, Cummings, and Larsen would not have rendered the claimed invention obvious to one of ordinary skill in the art when the invention was made.

D. Blann

Blann speculates that a compound differing in structure and mechanism from PSGL-1 (*e.g.*, aspirin) could be useful to treat thrombosis but does not teach that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis in a subject having hypertension. (Blann, page 608). There is no suggestion in Blann that PSGL-1, or the claimed fragments of PSGL-1, could be substituted for the compounds discussed in Blann, and Blann provides no reason to do so. Therefore Blann does not cure the deficiencies of Larsen and Cummings and would not have rendered the claimed invention obvious to one of ordinary skill in the art when the invention was made.

E. Araneo

Araneo discusses methods of treating ischemia and other conditions, including pulmonary hypertension, by administering the steroid DHEA, a very different compound from the instantly claimed protein. (*See Abstract; see also* column 4). Araneo does not

teach or suggest that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, but suggests reducing the level of P-selectin. (See column 17, lines 59-64). Similar to Blann, there is no reason provided by Araneo to substitute a composition comprising PSGL-1 for a completely different compound that exerts its activity in a different way. And, Araneo does not teach that hypertension is necessarily present in the conditions of Cummings or Larsen. Accordingly, Blann would not suggest that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis in a patient suffering from hypertension, and does not cure the deficiencies of Cummings and Larsen.

F. DeFrees

DeFrees describes analogs of sialyl Le^x, yet additional compounds that differ structurally and chemically from PSGL-1, and speculates about the use of these compounds to treat inflammatory disorders and deep vein thrombosis. (See column 3 and column 44, lines 35-65; see *also* column 45, lines 7-15). However, DeFrees fails to even mention hypertension, and does not provide any reason why the skilled artisan would substitute a composition comprising PSGL-1 for sialyl Le^x. Therefore, DeFrees does not cure the deficiencies of Cummings and Larsen, and would not render the claimed invention obvious to the skilled artisan at the time the invention was made.

G. The Merck Manual

As described above, and in detail in the Appeal Brief on pages 17-28, the Merck Manual merely describes a possible correlation between hypertension and certain conditions, but hypertension is just one of many risk factors that might predispose a patient to these conditions. Because one of ordinary skill in the art would not know

whether a patient suffering from a condition such as atherosclerosis also had hypertension, and none of the other publications cited by the Office show that a patient with hypertension necessarily had thromboses, one of skill in the art would have no reason to treat thromboses in a patient suffering from hypertension prior to Appellant's invention. Thus, the Merck Manual fails to cure the deficiencies of Cummings and Larsen.

Claim 27

H. Maugeri

Maugeri investigates how LTC_4 influences the aggregation of platelets and polymorphonuclear leukocytes, and describes decreased aggregation in the presence of an anti-P-selectin antibody. (See Introduction and Figure 2). Maugeri does not mention the use of a PSGL-1 to treat thrombosis, does not mention any relationship between thrombosis formation and hypertension, and does not provide any reason to attempt to substitute PSGL-1 for an anti-P-selectin antibody. Therefore, Maugeri would not have rendered claim 27, which recites LTC_4 , obvious at the time the invention was made.

I. Johnston

Johnston investigates the effect of anti-P-selectin antibodies on LTC_4 -induced leukocyte rolling (See, e.g., Figure 1). Johnston speculates about anti-inflammatory strategies designed to block leukocyte recruitment but does not identify the use of PSGL-1 and fails to teach or suggest any relationship between thrombus formation and hypertension. Johnson also fails to provide any reason to substitute PSGL-1 for an

antibody. Therefore, Johnston fails to cure the deficiencies of Larsen and Cummings, would not have rendered claim 27, which recites LTC₄, obvious.

Neither Larsen nor Cummings provide any reason for combining their teachings, and Blann, Araneo, DeFrees, Lip and the Merck Manual do not compensate for this deficiency, since none of these publications provide such a reason. Similarly, neither Maugeri nor Johnston compensate for the deficiencies of Larsen and Cummings because they also fail to discuss treating or preventing thrombosis in a subject having hypertension using a P-selectin ligand protein wherein thrombosis is induced by an thrombus inducing agent. Therefore, to one of skill in the art, Maugeri and Johnston would not render the claimed invention obvious. Appellant's understanding of the publications cited by the Office, and the non-obviousness of the claims in view of those publications, is supported by the Declaration. See Declaration, paragraphs 10-18.

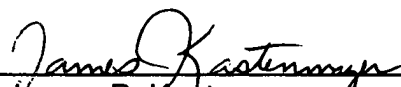
IV. Conclusion

For the reasons given above, pending claims 1-20, 25-27, 31-40, and 45, and 50-57 are allowable and reversal of the Examiner's rejection is respectfully requested.

Respectfully submitted,

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Dated: December 17, 2007

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